

Enantioselective Henry reaction catalyzed by C_2 -symmetric chiral diamine–copper(II) complex†

Sermadurai Selvakumar,^a Dhanasekaran Sivasankaran^a and Vinod K. Singh^{*a,b}

Received 2nd March 2009, Accepted 13th May 2009

First published as an Advance Article on the web 11th June 2009

DOI: 10.1039/b904254g

A copper(II) complex of C_2 -symmetric diamine has been proved to be an efficient catalyst for the enantioselective Henry reaction between nitroalkanes and various aldehydes to provide β -hydroxy nitroalkanes in high yields (up to 97%), moderate diastereoselectivities (up to 71:29) and excellent enantiomeric excesses (up to 96%). The chiral nitroaldol adduct obtained has been further converted into chiral aziridine in few steps.

Introduction

The Henry¹ (nitroaldol) reaction remains one of the most widely utilized transformations in synthetic organic chemistry. The enantioselective version of this reaction can provide access to important enantiomerically enriched β -nitroalkanol, which are versatile precursors for a wide range of important organic intermediates.² The nitro group in the product can be converted into amines (reduction), carbonyl compounds (Nef reaction),^{3c} azides (S_N2 displacement),^{2d} and other bifunctional compounds.³ However, despite its importance, the asymmetric Henry reaction was not explored until 1992. Shibasaki *et al.* reported the first example of asymmetric addition of nitromethane to aldehyde using a BINOL derived heterobimetallic complex.⁴ Since this pioneering work, the enantioselective Henry reaction has gained much attention and various types of chiral metal catalyst and organocatalyst⁵ have been extensively studied. Copper complexes of chiral ligands such as bis(oxazoline),⁶ (–)-sparteine,⁷ bisimidazoline,⁸ diamine,⁹ sulfonyldiamine,¹⁰ aminopyridine,¹¹ tetrahydroalene,^{12a} and N,N' -dioxide^{12b} have been developed for this reaction. Although a reasonable number of catalysts having metals other than copper, such as dinuclear zinc,^{13a} zinc triflate-amino alcohol,^{13b} zinc-bisoxazolidine,^{13c} zinc-fam catalyst,^{13d} cobalt-ketoimino complexes,¹⁴ nano-crystalline MgO,¹⁵ and salen-chromium complex¹⁶ have also been developed. Some of these methods have certain limitations such as high catalyst loading, the use of activated silylnitronates, low substrate scope, expensive starting materials, and long synthetic sequences for the ligand synthesis and the use of additives such as molecular sieves. Besides these, only a few catalytic systems have been tested for the diastereoselective Henry reaction. In this paper, we address some of these issues and delineate full details of our work in this area.

Results and discussion

The design, synthesis, and tuning of a suitable chiral ligand around a metal center is an important task in asymmetric synthesis.¹⁷ As a part of our research programme towards the application of versatile and fine tunable chiral non-racemic diamines in enantioselective reactions,¹⁸ we intended to evaluate similar kinds of amino acid derived diamine ligands (Fig. 1) for the enantioselective Henry reaction.

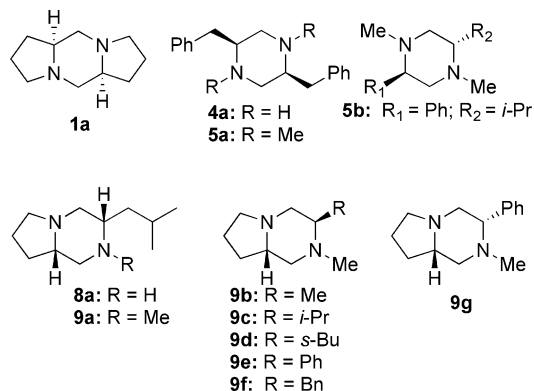


Fig. 1 Chiral diamine ligands.

A chiral C_2 -symmetric diamine **1a** is known in the literature and has been used for enantioselective alkylation of carbonyl compounds,^{19a} asymmetric benzoylation of 1,2-meso diols,^{19b} and enantioselective Baylis–Hillman reactions.^{19c,d} At the outset, it appeared logical to test this diamine in the Henry reaction. It was synthesized according to the known literature procedure starting from L-proline.^{19b} In order to optimize the reaction conditions, a series of reactions were carried out between nitromethane and benzaldehyde in ethanol with **1a**–Cu(OAc)₂·H₂O complex as the catalyst. The reaction was complete in 28 h at room temperature and the nitroaldol adduct was obtained in 74% ee (Table 1, entry 1). However, on decreasing the reaction temperature from rt to 0 °C and then to –20 °C, enantioselectivity increased remarkably with a decrease in the rate of the reaction (Table 1, entries 2 and 3). In order to improve the chemical yield of the reaction, without affecting the enantioselectivity, base promoter⁷ such as Et₃N were added for the activation of nitromethane. Thus, the catalyst

^aDepartment of Chemistry, Indian Institute of Technology, Kanpur, India 208 016. E-mail: vinodks@iitk.ac.in; Fax: +91-512-2597436; Tel: +91-512-2597291

^bIndian Institute of Science Education and Research Bhopal, ITI Campus (Gas Rahat) Building, Govindpura, India 460 023

† Electronic supplementary information (ESI) available: Experimental details, characterization data including ¹H NMR spectra, ¹³C NMR spectra for all compounds, and HPLC chromatograms for nitroaldol adducts. See DOI: 10.1039/b904254g

Table 1 Effect of the amount of Et₃N on the enantioselective Henry reaction^a

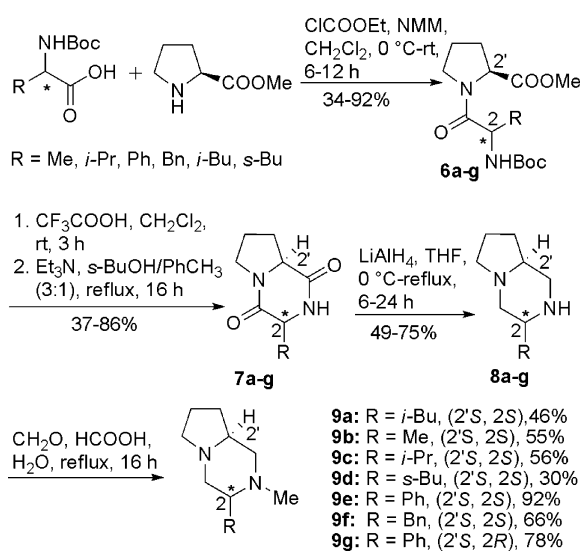
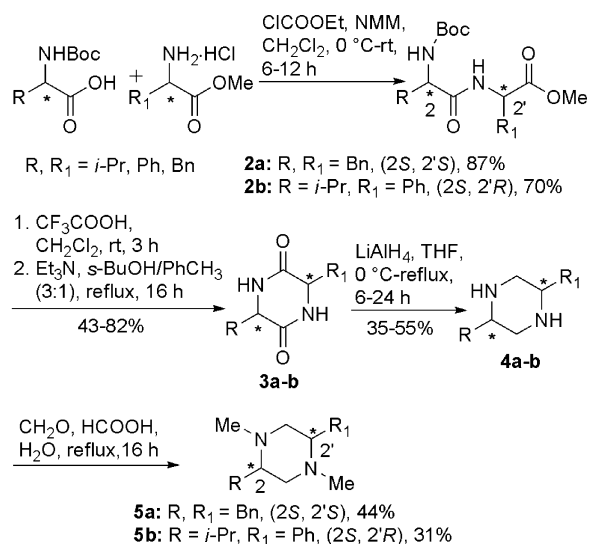
entry	Et ₃ N (mol%)	temperature (°C)	time (h)	yield (%)	ee ^b (%)
1	–	rt	28	86	74
2	–	0	62	28	86
3	–	–20	48	24	90
4	2	–20	62	32	90
5	5	–20	72	46	86
6	10	–20	36	70	88
7	20	–20	36	98	86
8	50	–20	24	97	75
9	100	–20	24	98	65
10	10	–40	96	75	92

^a Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane in 2 mL of ethanol. ^b Determined by chiral HPLC using Chiralcel OD-H column. The absolute configurations were established by comparison with literature data.

1a-Cu(II) complex was activated towards the Henry reaction under dual acid/base catalysis²⁰ conditions. It was gratifying to note that Et₃N increased the rate of the reaction without having a significant effect on the enantioselectivity. With 2 mol% of Et₃N at –20 °C, the reaction took longer and the corresponding product was obtained in 32% yield and 90% ee (Table 1, entry 4). However, on increasing the amount of Et₃N from 5 mol% to 20 mol%, the chemical yield of the reaction increased rapidly without affecting the enantioselectivity (Table 1, entries 5–7). Further increases in the amount of base resulted in the depletion of enantioselectivity (Table 1, entries 8 and 9). It was also observed that the use of 10 mol% of Et₃N and a reaction temperature of –40 °C are optimum for achieving high enantioselectivity in the reaction (Table 1, entries 6 and 10).

Having achieved good results in the above reaction with the ligand **1a**, it was logical to evaluate similar kinds of chiral piperazine derivative having mono- and bicyclic skeletons. With this aim, a variety of chiral diamines were synthesized. The generality of the synthesis was demonstrated in the preparation of these diamines in four steps from commercially available α -amino acids. The nature of the substituent at the stereocenter is dictated by the selection of the starting amino acid (Scheme 1). The coupling reaction of *N*-Boc amino acids with appropriate amino esters was carried out in the presence of ethylchloroformate and *N*-methylmorpholine. The Boc protecting group was then cleaved using TFA in CH₂Cl₂, which on subsequent reflux with Et₃N in 2-butanol:toluene (3:1) afforded diketopiperazine²¹ derivatives **3a–b** and **7a–g**. The diketopiperazines **3a–b** and **7a–g** obtained in this way were reduced to diamines **4a–b** and **8a–g** by using LiAlH₄. *N*-Methyl ligands **5a–b** and **9a–g** were synthesized by reductive amination^{21a} of formaldehyde with the diamines **4a–b** or **8a–g** in the presence of formic acid.

After successful completion of ligand synthesis, the chiral piperazines with monocyclic skeletons (Fig. 1) were first examined in the enantioselective Henry reaction under optimized conditions. Interestingly, the substituents on the nitrogen atoms of

**Scheme 1** Synthesis of chiral diamines.

phenylalanine-based diamines (**4a** vs **5a**) showed a significant effect on the enantioselectivity (Table 2, entries 2 and 3). Furthermore, only a trace amount of product was obtained in low enantioselectivity with diamine **5b** having different absolute stereochemistry (Table 2, entry 4). This clearly indicated that the matched chirality between the two amino acids is crucial for the high catalytic efficiency.

In order to study the effect of cyclic structures of diamine on enantioselectivity, diamines with bicyclic skeletons were then screened (Table 2, entries 5–12). A similar trend in enantioselectivity (*vide supra*) was observed after introducing a substituent on the nitrogen atom (Table 2, entries 2–3 vs 5–6). Next, the effect of variation in the substituents at the chiral centers of the bicyclic diamine ligands on the Henry reaction was studied. When the isobutyl group of the ligand **9a** was replaced by methyl, isopropyl, *sec*-butyl, benzyl or phenyl, the asymmetric induction in the reaction was scarcely affected (Table 2, entries 6–11). The absence of any asymmetric induction with ligand **9g** (Table 2, entry 12) indicated that both the stereogenic centers (*S,S*) of the diamine skeleton were essential for the chirality transfer in the catalytic

Table 2 Enantioselective Henry reaction of benzaldehyde with nitromethane in the presence of different ligands^a

entry	ligand	time (h)	yield (%)	ee ^b (%)
1	1a	96	75	92
2	4a	96	22	40
3	5a	102	47	77
4	5b	120	36	<i>rac</i>
5	8a	98	21	46
6	9a	102	61	89
7	9b	96	58	69
8	9c	96	63	75
9	9d	96	86	83
10	9e	144	53	39
11	9f	102	79	79
12	9g	144	44	<i>rac</i>

^a Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane and 0.05 mmol of base in 2 mL of ethanol. ^b Determined by chiral HPLC using Chiralcel OD-H column.

Table 3 Effect of different bases on the enantioselective Henry reaction^a

entry	base	time (h)	yield (%)	ee ^b (%)
1	Et ₃ N	96	72	92
2	Et(<i>i</i> Pr) ₂ N	72	86	82
3	<i>N</i> -methylmorpholine	72	14	87
4	pyridine	72	14	52
5	DMAP	48	11	17
6	1-methyl-1 <i>H</i> -imidazole	96	12	04
7	K ₂ CO ₃	48	34	18
8	DBU	96	72	59

^a Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane and 0.05 mmol of base in 2 mL of ethanol. ^b Determined by chiral HPLC using Chiralcel OD-H column.

Henry reaction (*vide supra*). From these results (Table 2), it was concluded that (*S*)-proline derived diamine **1a** with a tricyclic skeleton is superior in terms of yield and stereoselection (Table 2, entry 1) and was thus chosen for further studies.

The drastic effect of Et₃N on the rate of the reaction prompted us to examine the effect of other bases for this reaction. Among the bases screened, Et₃N gave the best result (Table 3, entry 1). The use of bulky tertiary amines like *i*Pr₂NEt and *N*-methylmorpholine gave lower enantioselectivity (Table 3, entries 2 and 3). Strong coordinating bases *viz* pyridine, DMAP and 1-methyl-1*H*-imidazole gave the product in poor chemical and optical yield (Table 3, entries 4–6). An inorganic base, K₂CO₃, gave poor results (Table 3, entry 7). Interestingly, the bulkier and more basic DBU gave the nitroaldol adduct in moderate yield and enantioselectivity (Table 3, entry 8).

Table 4 Effect of solvent on the enantioselective Henry reaction^a

entry	solvent	yield (%)	ee ^b (%)
1	methanol	59	63
2	ethanol	75	92
3	<i>n</i> -propanol	83	89
4	2-propanol	92	90
5	<i>n</i> -butanol	66	83
6	THF	39	83
7	acetonitrile	41	71
8	nitromethane	94	27 ^c
9	dichloromethane	24	73

^a Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane in 2 mL of solvent for 4 d. ^b Determined by chiral HPLC using Chiralcel OD-H column. ^c Reaction was carried out at –20 °C.

Table 5 Screening of Lewis acids for the enantioselective Henry reaction^a

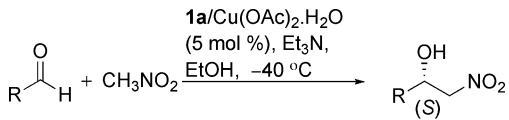
entry	Lewis acid	yield (%)	ee ^b (%)
1	Cu(OAc) ₂ ·H ₂ O	75	92
2	CuCl ₂	98	75
3	CuCl	51	37
4	Cu(OTf) ₂	94	75
5	Zn(OTf) ₂	17	<i>rac</i>
6	Zn(OAc) ₂ ·2H ₂ O	20	<i>rac</i>
7	Pd(OAc) ₂	06	16

^a Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane in 2 mL of ethanol for 4 d. ^b Determined by chiral HPLC using Chiralcel OD-H column.

The effect of solvent on the enantioselectivity in the Henry reaction catalyzed by diamine **1a** was also studied (Table 4). Among the different solvents screened, protic solvents were found to be superior to the aprotic ones, and of the different protic solvents screened, ethanol was the solvent of a choice (Table 4, entry 2).

A series of Lewis acids were then screened in combination with **1a** and Et₃N in ethanol (Table 5). Cu(OAc)₂·H₂O turned out to be the most suitable Lewis acid for the reaction. CuCl₂ and Cu(OTf)₂ also facilitated the reaction and afforded the nitroaldol adduct in excellent yield and moderate enantioselectivity (Table 5, entries 2 and 4). With other metal salts such as Zn(OTf)₂, Zn(OAc)₂·2H₂O and Pd(OAc)₂, reaction was sluggish and the product was almost racemic (Table 5, entries 5–7).

The scope and limitations of the Henry reaction catalyzed by **1a**–Cu(II) complex were then examined. A wide range of aldehydes including both aromatic and aliphatic aldehydes reacted smoothly with nitromethane under the optimized conditions, to give nitroaldol adduct in good yield and enantioselectivity²² (Table 6). The rate of the reaction with aromatic aldehydes

Table 6 Enantioselective Henry reaction of nitromethane with different aldehydes^a


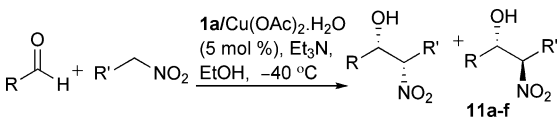
entry	R	time (h)	product	yield (%)	ee ^b (%)
1	C ₆ H ₅	96	10a	75	92
2	2-NO ₂ C ₆ H ₄	78	10b	91	87 ^c
3	4-NO ₂ C ₆ H ₄	78	10c	69	78 ^c
4	4-CF ₃ C ₆ H ₄	72	10d	60	90 ^c
5	4-FC ₆ H ₄	88	10e	97	89
6	3-MeC ₆ H ₄	94	10f	91	84
7	4-ClC ₆ H ₄	94	10g	93	85
8	4-MeC ₆ H ₄	116	10h	94	87
9	2-OMeC ₆ H ₄	90	10i	93	88
10	1-naphthyl	98	10j	70	80
11	2-MeC ₆ H ₄	94	10k	77	87
12	2-thienyl	98	10l	66	84
13	2-ClC ₆ H ₄	96	10m	94	84
14	3,5-OMeC ₆ H ₃	106	10n	88	87
15	3,4,5-OMeC ₆ H ₂	96	10o	90	83
16	PhCH ₂ CH ₂	120	10p	91	87 ^d
17	cyclohexyl	144	10q	42	93 ^d
18	3-pentyl	144	10r	51	96 ^d

^a Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane and 0.05 mmol of base in 2 mL of ethanol, unless noted otherwise. ^b Determined by HPLC using chiral column. ^c Reaction was carried out at -20 °C and in the absence of base. ^d 10 mol% of catalyst was used at 0 °C and in the absence of base.

containing electron-withdrawing groups (Table 6, entries 2–5) was faster in comparison to aldehydes having an electron-donating group (Table 6, entries 6–15). Under these conditions, the rate of the reaction was much slower for the aliphatic substrates. This was overcome by carrying out the reaction at 0 °C with 10 mol% of the catalyst and in the absence of Et₃N (Table 6, entries 16–18).

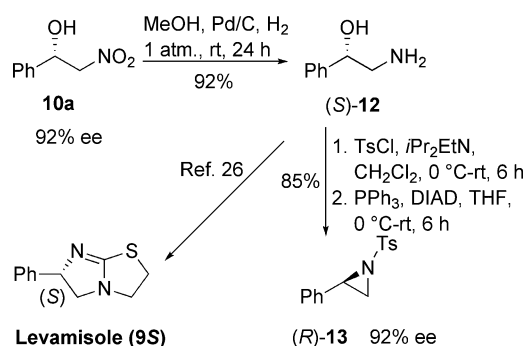
The catalytic activity of the **1a**-Cu(II) complex was tested for the diastereoselective Henry reaction, for which there are not many reports in the literature.^{9d,10,11b,13c} Under the optimized reaction conditions, aromatic aldehydes reacted with nitroethane to give nitroaldol product in moderate diastereoselectivity (up to 71: 29, *anti/syn*) and the *anti* product was formed predominantly, with an ee of 79% (Table 7, entry 1). On the other hand, reaction of nitroethane with aliphatic aldehyde afforded the *syn* isomer predominantly, with lower diastereoselectivity (54:46, *syn/anti*) and higher ee than the reaction of aromatic aldehydes (Table 7, entry 6).

With the nitroaldol adduct **10a** in hand, we found that it could be further elaborated into chiral amino alcohol (*S*)-**12**²³ through catalytic hydrogenation using 10% Pd/C in good yield (Scheme 2). The chiral amino alcohol thus obtained was then cyclised *via* sulfonylation followed by Mitsunobu reaction²⁴ with DIAD and PPh₃, readily furnished the corresponding aziridine (*R*)-**13** without loss of optical purity.²⁵ These aziridines constitute the key structural feature of several N-containing natural products and also serve in synthesis as chiral building blocks, auxiliaries, and ligands.²⁶ The chiral amino alcohol (*S*)-**12** is also a key intermediate in the synthesis of Levamisol (**9S**), an anthelmintic agent.²⁷

Table 7 Diastereoselective Henry reaction of nitroalkane with different aldehydes^a


entry	R	R'	time (h)	product	yield (%)	<i>syn/anti</i> ^b	ee (%) ^c <i>syn/anti</i>
1	C ₆ H ₅	Me	96	11a	78	38/62	80/79
2	2-MeC ₆ H ₄	Me	76	11b	70	29/71	79/66
3	2-OMeC ₆ H ₄	Me	72	11c	86	32/68	86/73
4	4-ClC ₆ H ₄	Me	78	11d	73	48/52	64/64
5	C ₆ H ₅	Et	144	11e	64	40/60	85/82
6 ^d	PhCH ₂ CH ₂	Me	144	11f	45	54/46	90/95

^a Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane and 0.05 mmol of base in 2 mL of ethanol, unless noted otherwise. ^b Determined by ¹H NMR analysis. ^c Determined by HPLC using chiral column. ^d 10 mol% of catalyst was used at 0 °C and in the absence of base.

**Scheme 2**

Conclusions

In conclusion, the chiral Cu(II)-**1a** complex prepared from Cu(OAc)₂·H₂O and the C₂-symmetric diamine ligand **1a** was found to be an effective catalyst for the enantioselective Henry reaction between nitroalkanes and aldehydes. The procedure is operationally very simple and can provide a variety of β-hydroxy nitroalkanes in good to excellent yields with excellent enantioselectivities (up to 96% ee). In addition, the chiral nitroaldol adduct has been derivatized to synthetically useful chiral aziridine in few steps.

Experimental section

General Methods

¹H and ¹³C NMR spectra were recorded on JEOL JNM-LA 400 and Jeol ECX 500 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in Hz. Mass spectrometric analyses were done on Waters Q Tof Premier Micromass (ESI) spectrometer. Routine monitoring of reactions was performed by TLC, using 0.2 mm Kieselgel 60 F₂₅₄ precoated aluminium sheets, commercially available from Merck. Visualization was done by fluorescence quenching at 254 nm, exposure to iodine vapor, and/or 2,4-dinitrophenylhydrazine solution. All the column chromatographic

separations were done by using silica gel (Acme's, 60–120 mesh). HPLC was done on a Daicel chiral column having 0.46 cm internal diameter \times 25 cm length. Petroleum ether used was of boiling range 60–80 °C. Reactions that needed anhydrous conditions were run under an atmosphere of nitrogen or argon using flame-dried glassware. The organic extracts were dried over *anhydrous* sodium sulfate. Evaporation of solvents was performed at reduced pressure. CH₂Cl₂, CHCl₃ and triethylamine (Et₃N) were distilled from CaH₂.

General procedure for the coupling of *N*-Boc amino acid with amino esters

A solution of (*S*)-*N*-Boc amino acid (10 mmol) and *N*-methylmorpholine (12 mmol) in CH₂Cl₂ (30 mL) was treated with ethyl chloroformate (12 mmol) at 0 °C for 10 min. Amino ester (12 mmol) was then added dropwise at the same temperature and the mixture was stirred for 16 h (0 °C to rt). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with CH₂Cl₂ (20 mL) and washed with water and brine. The organic layer was dried, and the solvent was evaporated in vacuo. Purification by column chromatography over silica gel gave pure coupled product **2** or **6**.

(*S*)-Methyl-1-((*S*)-2-(*tert*-butoxycarbonylamino)-4-methyl-pentanoil)pyrrolidine-2-carboxylate (6a). Yield 80%; Yellow liquid; [α]_D²⁵ -7.8 (*c* 1.0, CHCl₃); TLC *R*_f 0.60 (40%, EtOAc/Pet ether); IR ν_{\max} /cm⁻¹ (film) 3313, 2956, 1748, 1709, 1650; ¹H NMR (500 MHz, CDCl₃): δ 0.96 (m, 6H), 1.27 (m, 1H), 1.45 (s, 9H), 1.96 (m, 1H), 2.04 (m, 3H), 2.22 (m, 1H), 3.60 (m, 1H), 3.72 (s, 3H), 3.77 (m, 1H), 4.52 (m, 2H), 5.12 (d, *J* = 9.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 21.8, 23.4, 24.5, 24.9, 28.3, 28.9, 41.9, 46.7, 50.2, 52.2, 58.6, 79.5, 155.7, 171.9, 172.5. Anal. Calcd. for C₁₇H₃₀N₂O₅: C, 59.63; H, 8.83; N, 8.18. Found: C, 59.79; H, 8.85; N, 8.20.

General procedure for the synthesis of diketopiperazines

A solution of amide **2** or **6** (2.0 mmol) in dry CH₂Cl₂ (6 mL) was treated with TFA (800 μ L) at rt for 3 h. Solvent was then evaporated and the reaction mixture was dissolved in 2-butanol:toluene (4:2 mL) followed by addition of triethylamine (2 mmol). The mixture was allowed to reflux for 16 h. After the evaporation of solvent, diketopiperazines **3** or **7** precipitated as a white solid, which was filtered off, washed with MeOH, and used for next step without further purification.

(3*S*,8*aS*)-3-Isobutylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (7a). Yield 75%; White solid; mp 164 °C; [α]_D²⁵ -137.2 (*c* 0.5, DMSO); TLC *R*_f 0.50 (5%, MeOH/CH₂Cl₂); IR ν_{\max} /cm⁻¹ (pellet) 3429, 2993, 1670, 1634; ¹H NMR (400 MHz, CDCl₃): δ 0.99 (m, 6H), 1.54 (m, 1H), 1.78–2.15 (m, 5H), 2.35 (m, 1H), 3.57 (m, 2H), 4.02 (m, 1H), 4.12 (m, 1H), 6.30 (bs, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 21.3, 22.8, 23.3, 24.7, 28.1, 38.6, 45.5, 53.4, 59.0, 166.3, 170.3; HRMS (ES⁺) calc. for C₁₁H₁₈N₂O₂ 211.1446, [M + H]⁺ found 211.1445.

General procedure for the synthesis of piperazine

To a solution of amide (2 mmol) **3** or **7** in dry THF (8 mL) was added LAH (10 mmol) in portions at 0 °C and the reaction

stirred for 10 min. The reaction mixture was warmed slowly to room temperature and refluxed for 6–24 h. Reaction mixture was then cooled slowly to 0 °C and excess of LAH was destroyed by the addition of few drops of EtOAc. Water (200 μ L) was added, followed by the same amount of 4*N* NaOH. After 5 min, 600 μ L of water was again added and the mixture stirred for 15 min. The white precipitate formed was filtered off, the filtrate was dried, and solvent was evaporated. The crude product was purified by column chromatography using neutral alumina.

(3*S*,8*aS*)-3-Isobutyloctahydropyrrolo[1,2-*a*]pyrazine (8a). Yield 74%; Colorless liquid; [α]_D²⁵ +12.8 (*c* 1.0, CHCl₃); IR ν_{\max} /cm⁻¹ (film) 3286, 2953; ¹H NMR (400 MHz, CDCl₃): δ 0.90 (m, 6H), 1.28 (m, 1H), 1.47 (m, 1H), 1.62–1.83 (m, 5H), 2.02 (m, 1H), 2.2–2.33 (m, 2H), 2.64–2.77 (m, 2H), 2.91–2.97 (m, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 20.7, 22.2, 23.1, 24.9, 26.7, 41.0, 45.6, 50.4, 54.6, 57.0, 63.2; HRMS (ES⁺) calc. for C₁₁H₂₂N₂ 183.1861, [M + H]⁺ found 183.1861.

General procedure for the reductive amination of piperazines

To a solution of amine **4** or **8** (2.5 mmol) in water (2.5 mL) was added formaldehyde (8.5 mmol, 39% in w/v) and formic acid (27.5 mmol) at room temperature. The reaction mixture was allowed to reflux for 16 h. It was cooled and then basified by the addition of saturated NaHCO₃ and 10*N* NaOH solution. Aqueous layer was extracted with EtOAc and the organic layer was then washed with brine and dried over *anhydrous* Na₂SO₄. Solvent was removed in vacuum and the residue was purified by column chromatography using neutral alumina.

(3*S*,8*aS*)-3-Isobutyl-2-methyloctahydropyrrolo[1,2-*a*]pyrazine (9a). Yield 46%; Colorless liquid; [α]_D²⁵ +26.3 (*c* 0.6, CHCl₃); TLC *R*_f 0.50 (100%, MeOH); IR ν_{\max} /cm⁻¹ (film) 2954, 2794; ¹H NMR (400 MHz, CDCl₃): δ 0.89 (m, 6H), 1.25–1.84 (m, 7H), 2.10 (m, 2H), 2.27–2.38 (m, 5H), 2.61 (m, 2H), 2.81 (dd, *J* = 2.4, 10.8 Hz, 1H), 2.95 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 21.1, 22.0, 23.6, 26.3, 27.4, 32.9, 42.2, 53.9, 54.0, 54.9, 57.3, 62.2; HRMS (ES⁺) calc. for C₁₂H₂₄N₂ 197.2018, [M + H]⁺ found 197.2018.

General procedure for the enantioselective/diastereoselective Henry reaction

A solution of ligand **1a** (4.6 mg, 0.0275 mmol) and Cu(OAc)·H₂O (5 mg, 0.025 mmol) in dichloromethane (2 mL) was stirred overnight at room temperature. Solvent was removed under reduced pressure and the residue was dissolved in dry EtOH (2 mL). To the resulting blue solution, nitroalkane (5 mmol), Et₃N (7 μ L, 0.050 mmol) and aldehyde (0.5 mmol) were added at -40 °C. The reaction mixture was stirred for appropriate time and the progress of the reaction monitored by TLC. After completion of the reaction, the volatile components were removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/Petroleum ether) to afford the nitroaldol product. The enantiomeric excess was determined by chiral HPLC and diastereoselectivity was determined by ¹H NMR spectroscopy.

Synthesis of (*S*)-2-amino-1-phenylethanol (12). β -Nitro alcohol **10a** (0.4 mmol) in methanol (2 mL) was hydrogenated (H₂, 1 atm) in the presence of 10% Pd/C (20 mg) for 24 h. The solution was filtered over celite, and the methanol was removed under

reduced pressure. The crude material was used without further purification. Yield 92%; white solid; mp 54–56 °C; $[\alpha]_{\text{D}}^{25} +9.1$ (*c* 1.68, EtOH); [lit.²³ (*S*) ee = 100%; $[\alpha]_{\text{D}}^{20} +47.9$ (*c* 2.4, EtOH)]; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3384, 2925, 2855; ¹H NMR (500 MHz, CDCl₃): δ 2.79 (m, 1H), 3.0 (m, 1H), 3.46 (bs, 1H), 4.63 (m, 1H), 7.25–7.36 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): δ 49.3, 74.4, 125.9, 127.6, 128.5, 128.6, 142.6; HRMS (ES+) calc. for C₈H₁₁NO 138.0920, [M + H]⁺ found 138.0919.

Synthesis of (R)-2-phenyl-1-tosylaziridine (13). *p*-Toluene sulfonyl chloride (1.2 mmol) was added in portions to a solution of amino alcohol **12** (1 mmol) and diisopropylethylamine (2 mmol) in CH₂Cl₂ (4 mL) at 0 °C. The ice bath was then removed, and the reaction was allowed to warm to rt and further stirred for 6 h. The reaction mixture was then washed with water, brine and dried over *anhydrous* Na₂SO₄. The organic layer was then concentrated and the crude product was purified by column chromatography on silica gel to afford the sulfonylated amino alcohol. To this *N*-sulfonyl-substituted amino alcohol in dry THF (4 mL) was added triphenylphosphine (1.2 mmol) in one portion at rt. The reaction mixture was then cooled to 0 °C, and treated slowly with diisopropylazodicarboxylate (1.2 mmol). The ice bath was removed and the yellow solution was stirred at rt for 6 h. THF was evaporated, and the residue was purified by column chromatography to yield the chiral aziridine **13**. Yield 85%; white solid, mp 82–84 °C; TLC R_f 0.8 (40% EA in petroleum ether); $[\alpha]_{\text{D}}^{25} -86.4$ (*c* 1.0, CHCl₃); IR $\nu_{\text{max}}/\text{cm}^{-1}$ (pellet) 3038, 1385; ¹H NMR (500 MHz, CDCl₃): δ 2.38 (m, 1H), 2.42 (s, 3H), 2.98 (m, 1H), 3.77 (m, 1H), 7.2–7.33 (m, 7H), 7.87 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 21.8, 36.1, 41.1, 126.7, 128.0, 128.4, 128.7, 129.9, 135.0, 135.1, 144.8; HRMS (ES+) calc. for C₁₅H₁₅NO₂S 274.0902, [M + H]⁺ found 274.0903; Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (*n*-hexane/2-propanol 90:10, λ = 254 nm); flow rate 0.8 mL/min; *t*_{R(minor)} = 37.47 min (*S*), *t*_{R(major)} = 44.43 min (*R*).

Acknowledgements

V.K.S. thanks the Department of Science and Technology, India for a research grant through J.C. Bose fellowship. S.S. and D.S. thank the Council of Scientific and Industrial Research, New Delhi for research fellowships.

Notes and references

- 1 L. Henry, *C. R. Hebd. Seances Acad. Sci.*, 1895, **120**, 1265.
- 2 (a) L. Allmendiger, G. Bauschke and F. F. Paintner, *Synlett*, 2005, 2615; (b) N. Gogoi, J. Boruwa and N. C. Barua, *Tetrahedron Lett.*, 2005, **46**, 7581; (c) F. F. Paintner, L. Allmendiger, G. Bauschke and P. Klemmann, *Org. Lett.*, 2005, **7**, 1423; (d) H. Li, B. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 732.
- 3 (a) D. Seebach, A. K. Beck, T. Mukhopadhyay and E. Thomas, *Helv. Chim. Acta*, 1982, **65**, 1101; (b) G. Rosini, In *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming and C. H. Heathcock, Eds.; Pergamon, New York, 1996; Vol. 2, pp 321; (c) F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915; (d) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001.
- 4 (a) H. Sasai, T. Suzuki, S. Arai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418; (b) T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai and M. Shibasaki, *Chem.-Eur. J.*, 1996, **2**, 1368; (c) N. Yoshikawa and M. Shibasaki, *Chem. Rev.*, 2002, **102**, 2187; (d) S. Handa, K. Nagawa, Y. Sohtome, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2008, **47**, 3230.

- 5 (a) E. J. Corey and F.-Y. Zhang, *Angew. Chem., Int. Ed.*, 1999, **38**, 1931; (b) T. Ooi, K. Doda and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 2054; (c) H. Li, B. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 732; (d) T. Marcelli, R. N. S. Van, der Haas, J. H. Van Maarseveen and H. Hiemstra, *Angew. Chem., Int. Ed.*, 2006, **45**, 929; (e) Y. Sohtome, Y. Hashimoto and K. Nagasawa, *Eur. J. Org. Chem.*, 2006, 2894; (f) T. Mandal, S. Samanta and C. -G. Zhao, *Org. Lett.*, 2007, **9**, 943; (g) D. Uraguchi, S. Sakaki and T. Ooi, *J. Am. Chem. Soc.*, 2007, **129**, 12392.
- 6 (a) C. Christensen, K. Juhl and K. A. Jørgensen, *Chem. Commun.*, 2001, 2222; (b) C. Christensen, K. Juhl, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 4875; (c) K. V. Risgaard, K. A. Gothelf and K. A. Jørgensen, *Org. Biomol. Chem.*, 2003, **1**, 153; (d) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692; (e) S. F. Lu, D. M. Du, S. W. Zhang and J. X. Xu, *Tetrahedron: Asymmetry*, 2004, **15**, 3433; (f) D. M. Du, S. F. Lu, T. Fang and J. X. Xu, *J. Org. Chem.*, 2005, **70**, 3712; (g) S. K. Ginotra and V. K. Singh, *Org. Biomol. Chem.*, 2007, **5**, 3932; (h) A. Toussaint and A. Pfaltz, *Eur. J. Org. Chem.*, 2008, 4591.
- 7 H. Maheswaran, K. L. Prasant, G. G. Krishna, K. Ravikumar, B. Sridhar and M. L. Kantam, *Chem. Commun.*, 2006, 4066.
- 8 K. Ma and J. You, *Chem.-Eur. J.*, 2007, **13**, 1863.
- 9 (a) T. Arai, M. Wantanabe, A. Fujiwara, N. Yokayama and A. Yanagisawa, *Angew. Chem., Int. Ed.*, 2006, **45**, 5978; (b) M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi and C. Ventrici, *Chem. Commun.*, 2007, 616; (c) M. Bandini, M. Benaglia, R. Sinisi, S. Tommasi and A. Umani-Ronchi, *Org. Lett.*, 2007, **9**, 2151; (d) T. Arai, M. Watanabe and A. Yanagisawa, *Org. Lett.*, 2007, **9**, 3595.
- 10 T. Arai, R. Takashita, Y. Endo, M. Watanabe and A. Yanagisawa, *J. Org. Chem.*, 2008, **73**, 4903.
- 11 (a) G. Blay, E. Climent, I. Fernández, V. Hernández-Olmos and J. R. Pedro, *Tetrahedron: Asymmetry*, 2007, **18**, 1603; (b) G. Blay, L. R. Domingo, V. Hernández-Olmos and J. R. Pedro, *Chem.-Eur. J.*, 2008, **14**, 4725.
- 12 (a) Y. Xiong, F. Wang, X. Huang, Y. Wen and X. Feng, *Chem. Eur. J.*, 2007, **13**, 829; (b) B. Qin, X. Xiao, X. Liu, J. Huang, Y. Wen and X. Feng, *J. Org. Chem.*, 2007, **72**, 9323.
- 13 (a) B. M. Trost and V. S. C. Yeh, *Angew. Chem., Int. Ed.*, 2002, **41**, 861; (b) C. Palomo, M. Oiarbide and A. Laso, *Angew. Chem., Int. Ed.*, 2005, **44**, 3881; (c) S. Liu and C. Wolf, *Org. Lett.*, 2008, **10**, 1831; (d) A. Bulut, A. Aslan and O. Dogan, *J. Org. Chem.*, 2008, **73**, 7373.
- 14 (a) Y. Kogami, T. Nakajima, T. Ashizawa, S. Kezuka, T. Ikeno and T. Yamada, *Chem. Lett.*, 2004, 614; (b) Y. Kogami, T. Nakajima, T. Ikeno and T. Yamada, *Synthesis*, 2004, 1947.
- 15 B. M. Choudary, K. V. S. Ranganath, U. Pal, M. L. Kantam and B. Sreedhar, *J. Am. Chem. Soc.*, 2005, **127**, 13167.
- 16 (a) R. Kowalczyk, P. Kwiatkowski, J. Skarzewski and J. Jurczak, *J. Org. Chem.*, 2009, **74**, 753; (b) A. Zulauf, M. Mellah and E. Schulz, *J. Org. Chem.*, 2009, DOI: 10.1021/jo802769y.
- 17 R. Noyori, *Asymmetric Catalysis in Organic synthesis*, Wiley, New York, 1994.
- 18 (a) D. Bhuniya, A. Dattagupta and V. K. Singh, *Tetrahedron Lett.*, 1995, **36**, 2847; (b) D. Bhuniya, A. Dattagupta and V. K. Singh, *J. Org. Chem.*, 1996, **61**, 6108; (c) P. Saravanan and V. K. Singh, *Tetrahedron Lett.*, 1998, **39**, 167; (d) V. Maya and V. K. Singh, *Org. Lett.*, 2007, **9**, 1117.
- 19 (a) G. Zadel and E. Breitmaier, *Chem. Ber.*, 1994, **127**, 1323; (b) D. Nakamura, K. Kakiuchi, K. Koga and R. Shirai, *Org. Lett.*, 2006, **8**, 6139; (c) H. Tang, G. Zhao, Z. Zhou, Q. Zhou and C. Tang, *Tetrahedron Lett.*, 2006, **47**, 5717; (d) H. Tang, G. Zhao, Z. Zhou, P. Gao, L. He and C. Tang, *Eur. J. Org. Chem.*, 2008, 126.
- 20 (a) G. J. Rowlands, *Tetrahedron*, 2001, **57**, 1865; (b) H. Groger, *Chem.-Eur. J.*, 2001, **7**, 5247; (c) M. Shibasaki and N. Yoshikawa, *Chem. Rev.*, 2002, **102**, 2187; (d) M. Shibasaki, M. Kanai and K. Funabashi, *Chem. Commun.*, 2002, 1989; (e) J.-A. Ma and D. Cahard, *Angew. Chem., Int. Ed.*, 2004, **43**, 4566.
- 21 (a) J. C. Rohloff and M. E. Jung, *J. Org. Chem.*, 1985, **50**, 4909; (b) B. McKeever and G. Pattenden, *Tetrahedron*, 2003, **59**, 2701; (c) A. Boruah, N. I. Rao, J. P. Nandy, S. K. Kumar, A. C. Kunwar and J. Iqbal, *J. Org. Chem.*, 2003, **68**, 5006; (d) J. P. Cain, A. V. Mayorov, M. Cai, H. Wang, B. Tan, K. Chandler, Y. Lee, R. R. Petrov, D. Trivedi and V. J. Hruby, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5462; (e) T. Tullberg, M. Grotli and M. K. Luthman, *Tetrahedron*, 2006, **62**, 7484.

-
- 22 The reaction of ethyl benzoylformate with nitromethane under standard conditions gave nitroaldol product in 70% yield with 10% ee.
- 23 B. T. Cho, S. K. Kang and S. H. Shin, *Tetrahedron: Asymmetry*, 2002, **13**, 1209.
- 24 For a review see: O. Mitsunobu, *Synthesis*, 1981, 1.
- 25 M. Nishimura, S. Minakata, T. Takahashi, Y. Oderaotoshi and M. Komatsu, *J. Org. Chem.*, 2002, **67**, 2101.
- 26 (a) D. Tanner, *Angew. Chem., Int. Ed.*, 1994, **33**, 599; (b) R. S. Atkinson, *Tetrahedron*, 1999, **55**, 1519; (c) W. McCoull and F. A. Davis, *Synthesis*, 2000, 1347; (d) J. B. Sweeney, *Chem. Soc. Rev.*, 2002, **31**, 247; (e) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701; (f) D. Morton and R. A. Stockman, *Tetrahedron*, 2006, **62**, 8869; (g) I. D. G. Watson, L. Yu and A. K. Yudin, *Acc. Chem. Res.*, 2006, **39**, 194; (h) X. L. Hou, J. Wu, R. H. Fan, C. H. Ding, Z. B. Luo and L. X. Dai, *Synlett*, 2006, 181; (i) S. Gandhi, A. Bisai, B. A. Prasad and V. K. Singh, *J. Org. Chem.*, 2007, **72**, 2133; (j) K. Kawamura, H. Fukuzawa and M. Hayashi, *Org. Lett.*, 2008, **10**, 3509.
- 27 A. Kamal, G. B. R. Khanna, T. Krishnaji and R. Ramu, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 613.